REMARKS

Claims 10-19 and 25-26 are currently pending in the application. Claims 10 and 15-19 are amended herein. New claims 25 and 26 have been added herein. Claims 11-13 are canceled herein. Claim 19 of Group III, which was previously elected for restriction in Applicant's December 14, 2005 Response to Restriction Requirement, has been rejoined with Group II (claims 10-18).

In the specification, the paragraphs beginning on page 32, lines 9 through 12 and page 24, lines 3-17 have been amended to correct prior art references cited in the original application. The amendments in the specification merely correct the name of the author from "Colowick, et al." to "Wu and Grossman Eds.", and incorporate the year "1996" to the cited White, et al. article.

PRIORITY

The Examiner has acknowledged the domestic claim for priority put forward in the last Amendment. Applicants gratefully acknowledge this action on the part of the Examiner.

ELECTION/RESTRICTIONS

Applicants respectfully acknowledge and thank the Examiner for her rejoining of Groups II and III of the present application. Claims 10-19 and 25-26 are currently pending in the application.

INFORMATION DISCLOSURE STATEMENT

A replacement copy of the PTO Form 1449 filed December 13, 2004 as requested by the Examiner is submitted herewith. Page 12/12 has been corrected to incorporate the following changes: the "Colowick et al." reference has been amended to indicate the correct author, "Wu and Grossman Eds.," and the cited "White" article now includes the missing year "1996." Respectfully, these amendments overcome the Examiner's objection to the Information Disclosure Statement.

CLAIM AMENDMENTS

Applicants wish the Examiner to take note that their representation before the USPTO has recently changed since this application was filed. This change in representation has necessitated a review of the specification and prior prosecution activities by their new attorney. During this review it was determined that substantial amendments to the claims were needed to answer the Examiner's objections and to more fully present the invention for examination. Therefore each of the pending claims have been amended or have been added by Applicant in this Response. The pending claims as provided by Applicant are thus intended to be both part of a fully responsive reply to the Examiner's rejections and fully grounded in the teachings of the specification. MPEP §§ 608.01; 714.

Applicants believe that the amendments which have been made, along with the extensive nature of this response serve to put all the remaining claims in better condition for allowance. This is also true with respect to the canceled claims as well as with the claims which were amended or added. Given the above, it is specifically and respectfully requested that the Examiner enter and allow the claims as amended herein.

CLAIM REJECTIONS – 35 USC §101

Claims 10-13 and 16-19 stand rejected under 35 USC § 101 as being directed to non-statutory matter. To overcome this rejection, claims 10, and 17-19 have been amended to cite appropriate statutory matter (i.e., "non-human") as suggested by the Examiner. The pending claims as a whole are now believed to comply with the provisions of 35 U.S.C. § 101. Thus, the Examiners rejection of these claims, based on §101 is overcome. Reconsideration of the pending claims is therefore respectfully requested.

CLAIM REJECTIONS – 35 USC §112, FIRST PARAGRAPH

Claims 10 through 19 are rejected under 35 U.S.C. §112, first paragraph. The Examiner's contention is that the application as filed is not enabling for "any preparation of any transgenic decorin, wherein any preparation comprising any transgenic decorin is obtained from any transgenic organism comprising any transgene that directs expression

of decorin or from any product produced by said organism." (Office Action of 2/10/2005, page 3 second full paragraph).

With regard to the disclosure presented in the current application, these rejections have been addressed by a series of amendments to the claims to more particularly point out the novelty of the current invention and provide limits to the claims as reflected in the specification.

Experimentation

It must stated that the specification, to the limited extent it is necessary in the instant case, is not required to teach every detail of the invention or to perform the function of a technical production manual/specification. The specification need only explain how to make and use the invention without requiring an inordinate amount of experimentation. Moreover, even the possibility that experimentation needed may be complex does not necessarily make it undue if a person skilled in the art typically engages in such experimentation. In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970). In fact, enablement itself is a legal issue (citations omitted), and the issue is resolved by asking the question whether or not the instant disclosure is, coupled with the prior art sufficient to enable those skilled in the art to practice the claimed invention. In this way a specification need only present those elements of the invention which are novel, avoiding the need to supply a vast treatise on a given area of technology every time an application is filed. The prior art therefore is available and expected to fill any gaps that the instant specification might have with regard to enablement. In re Myers, 410 F.2d 420, 161 USPQ 668 (CCPA 1969). Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984); Ajinomoto Co., Inc. v. Hering-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999); *and see*, Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

The working examples provided in the specification, and the functional identity of the recombinant decorin molecule provides the assurance that any needed

experimentation will not be "undue" and will amount to little more than routine optimization.

In a broad sense the novelty of the patent lies, as expected, in the novel manipulation and engineering of the decorin molecule, its physiological activity. The fact that the prior art did not contemplate the generation and use of the recombinant decorin of the invention, while the Applicants provide and claim a working example and a written protocol of such is the precise reason why the current application is patentable -- it is novel.

The extensive protocols disclosed in the specification, provide the public the ability to practice the invention, by providing a detailed map leading towards a goal that has already been reached, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant case law discussed above, does provide "adequate" guidance to make and use the invention. In re Vaeck, 947 F.2d 488, at 496 (Fed. Cir. 1991).

Indeed, the application presents the essential features of the molecular manipulations necessary to carry out the invention. Moreover, the Applicants eliminate the need for any undue experimentation by providing examples in the specification. This level of disclosure is **more than** what is necessary for a specification to provide. In determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and U.S. patents. Whereupon, the disclosure of a relevant discovery, and subsequent allowance as a patent, would then provide a variety of potential uses for those skilled in the art, as mentioned above. With regard to the nature of the specification in the instant matter, the uses therein disclosed need not be apparent to everyone, all that is required is that enablement, and the potential usefulness of the discovery is communicated to the skilled artisans of the relevant technology. Respectfully the Applicants maintain that this communication was sufficiently performed in the specification. Therefore, the Examiners rejection of the claims under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882).

In view of the foregoing, it is respectfully submitted that the disclosure provided in the instant specification complies fully with the requirements of § 112, first paragraph and the amended claims in that the description of the various laboratory protocols needed and employed to develop a line of non-human transgenic mammal producing a human decorin in their milk is provided in a full, clear and concise way open to any person skilled in the art enabling one to make and use the recombinant decorin product without undue experimentation.

It is respectfully suggested that Applicants have shown that amended independent claims 10 and 18 are enabled. Dependent claims 14-17 and 19 being dependent upon and further limiting these independent claims should be allowable for that reason. Reconsideration of the rejection is respectfully requested. New claims 25 and 26 are dependent upon independent base claim 10. This independent claim along with the second independent claim 18 have been amended or crafted in light of the Examiners concerns and suggestions. As they contain all the elements of the amended independent claim 10 and additional elements they should be allowable for that reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 25-26.

CLAIM REJECTIONS – 35 USC §102

Claims 10 stands rejected under 35 USC § 102 as being anticipated by Hering et al. Respectfully, with the amendment of claim 10 to narrower subject matter this rejection is overcome.

Generally, anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference or embodied in a single prior art device or practice. *See,* In re Spada, 911 F.2d 705, 15 U.S.P.Q.2d 1655 (Fed Cir. 1990); *See also,* Minnesota Min. & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc., 976 F.2d 1559, 24 U.S.P.Q.2d (Fed Cir. 1992). Anticipation requires **both an identity of elements and identity of process,** this Hering et al., is incapable of providing. Tyler Refrigeration v. Kysor Indus. Corp., 777 F.2d 687, 227 U.S.P.Q.177 (Fed Cir. 1986). As

was stated by the 9th Circuit:

> "Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in prior pleaded art, there is no anticipation." Stauffer v. Slenderella Systems of California, Inc., 254 F.2d 127, 115 USPQ 347 (9th Cir. 1957).

It must be remembered that for anticipation to be properly found it is necessary that a previous disclosure express the virtually identical presence and function of the claimed methods and assays, thereby putting the invention in the hands of the public to practice. That is, guiding precedent states that if a given reference does not teach how to use the invention to the public, no anticipation can be found. In re Wilder, 429 F.2d 447, 166 USPQ 545 (C.C.P.A. 1964); In re Brown, 329 F.2d 1006, 141 USPQ 245 (C.C.P.A. 1964); In re LeGrice, 301 F.2d 929, 133 USPQ 365 (C.C.P.A. 1962). This is clearly not done with the Hering reference. Respectfully, the Hering reference does not "inherently" or even inferentially disclose the instant invention, or read on any of its amended claims. Moreover, to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362; 52 U.S.P.Q.2D 1303 (1999).

Therefore, in order to avoid rejection for anticipation, it is only necessary to show that independent base claims 10 contains at least one element not disclosed in Hering et al. In reviewing the teachings of the Hering et al., reference, as guided by the prior legal precedent cited above, it is clear that the claims not only fail to recite the same elements, the actual function or "process" of utilizing the elements differs considerably. Rather, Hering recites "bacterial cells" with the "bovine" protein of interest being harvested through the "lysis" of cells "grown in culture" none of which resemble, replace or suggest any of the elements present in the instant application and recited in the claims. More specifically, claim 10 recites several elements not present or suggested in any of the teachings of Hering et al., including:

a) Non-human transgenic mammals;

b) Recombinant human decorin;

and,

c) milk;

None of the elements a-c above are disclosed in the Hering et al., reference. Therefore, it is respectfully proposed that the rejection of claim 10 for anticipation by the Hering et al., reference is overcome. The remaining dependent claims 14-17 and 19 being dependent upon and further limiting independent claim 10, should also be allowable for that reason, as well as for the additional recitations they contain. Reconsideration of the rejection of amended claims under 35 U.S.C. § 102, is respectfully requested.

New claims 25 and 26 are dependent upon independent amended claim 10. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 25 and 26 under 35 U.S.C. § 102, in view of the above amendments and remarks.

CLAIM REJECTIONS – 35 USC §103

Houdebine et al., Krusius et al., Ruoslahti et al., Mann et al., and Roberts et al.,

Claims 10 – 19 are rejected under 35 U.S.C §103(a) as being unpatentable over Houdebine et al., in view of Krusius et al., Ruoslahti et al., Mann et al., and Roberts et al. Claims 11-13 are canceled herein. Independent claims 10 and 18 have been extensively amended herein. In particular, Applicants point to the amendments to the independent claims in response to the Examiner's rejections. It should be noted at the outset that the primary existing independent claim (claim 10) has been substantially amended herein to address a variety of the Examiner's concerns and has included new limitations on breadth the Applicant believes takes well outside any anticipation or obviousness rejection based

on the Houdebine citation or other references. Therefore Applicant requests reconsideration of the claims in light of these amendments

At the outset it should be stated that Applicants purposefully employed a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of specific hormonally induced proteins (e.g., milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount, in this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." Not only did the Applicants use this system they increased its power and complexity by making a significant scale-up of the process possible with the use of a promoter sequence activated in the mammary gland.

As presented above neither Houdebine et al., nor Ruoslahti – or the other cited references provide sufficient guidance along this line to negative patentability.

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993). The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;
(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). As pointed out above, the cited references not only fail to render obvious the current claims standing alone they also fail to render them obvious when taken together.

Ruoslahti

The prior art cited by the Examiner is simply insufficient to render the amended claims unpatentable. Ruoslahti et al., relates to the use of cell culture / *in vitro* derived decorin. However, these citations ignore the activities of those skilled in the art at the time of this invention. More to the point, Ruoslahti *et al.,* do not disclose and are in fact silent with regard to any meaningful instruction with regard to the techniques needed or problems associated with the inclusion of any nucleic acid construct in the cells of a host transgenic mammal leading to the expression of a biologically active construct. The citations also fail to mention any teaching with regard to the expression or recovery of proteins from the milk of transgenic mammals.

Instead, Ruoslahti *et al.*, provides a primer on the use of decorin exemplified exclusively through production through *in vitro* methods. In this light the citations are simply incapable of supporting the rejection of the instant claims. Going further, the Examiner's analysis inappropriately bases its rejection on the use of Ruoslahti *et al.*, on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein for any biologically active molecule is an appropriate and analogous prior art reference for the claimed invention of another such expression system. This is simply not the case.

Rather the inventors seek to provide a means to reliably producing a protein through a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of a specific hormonally induced protein (e.g., decorin in the milk and milk proteins of a transgenic mammal) in incredibly high concentration and pushes them out of the system of a whole animal in a regular

reliable amount, in this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." Ruoslahti simply provides no guidance along this line, and is in fact, completely silent with regard to any differences in various expression systems. Moreover, along with the strength and peculiarities of transgenic mammals as "bio-reactors" the instant invention also provided solutions to a host of expression problems lamented in the prior art, but never overcome by it.

The invention of the Appellants required a systematic understanding of the host of problems seen before in the prior art and a novel way of using a variety of complex tools to produce the raw material for a new class of molecule produced in a novel way. Something which quite simply had not been done before, or reduced to practice with regard to the decorin molecule.

In addition, each of the rejections to individual claims has been addressed through specific amendment to the relevant claims to clarify, particularly point out, and distinctly claim the subject matter of the invention relative to the prior art cited by the Examiner. Reconsideration of the rejection of amended claims 10, 14, 18-19 under 35 U.S.C. § 103(a) is respectfully requested.

New claims 25 and 26 carry limitations similar to those found in amended independent claims 10 and 18. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 25 and 26 under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

No fee is deemed necessary in connection with the filing of this Reply and Amendment. However, the Commissioner is authorized to apply any fee which may now be or hereafter be due for this application to Deposit Account No. 502092.

Early and favorable action is earnestly solicited.

Respectfully submitted,

Date: 9/2/05

By: _____

Byron V. Olsen, Reg. No. 42,960
ATTORNEY FOR APPLICANT
GTC Biotherapeutics, Inc.
175 Crossing Blvd., Suite 410
Framingham, MA 01702
Tel. # (508) 370-5150
Fax # (508) 370-3797